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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/021,002	12/19/2001	Wei-Wu He	PF150D2	9797

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/021,002	HE ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 41-64 are being examined.

The following are the remaining rejections.

DEPOSIT REQUIREMENT

The Deposit requirement is maintained because although Applicant submits a statement reciting that all restrictions upon public access to the deposits will be irrevocably removed upon the granting of a patent on this application, however, Applicant recites that the assignee of the present application "has been notified" of its responsibility to replace the deposited biological material, should the deposited material be destroyed or rendered non-viable, without further reciting that the deposit "will be replaced" if viable samples cannot be dispensed by the depository.

It is noted that the requirement is that the deposit "will be replaced" if viable samples cannot be dispensed by the depository.

See 37 CFR 1.803-1.809 for additional explanation of these requirements.

Claim 53 remains rejected under USC 112, first paragraph, for the reasons set forth in the objection to the specification.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Rejection under 35 USC 112, second paragraph of claims 44, 56 pertaining to the use of the indefinite language "a chimeric antibody" remains for reasons already of record in paper of 12/02/04.

Applicant argues that the claims are intended to refer to the most common usages of the term "chimeric antibody", i.e. antibodies having variable regions from non-human antibodies and human constant regions or to antibodies having CDRs from non-human antibodies and framework and constant regions from human antibodies.

Applicant's arguments set forth in paper of 03/02/05 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the term "chimeric antibody" is generic to any antibody which contains antibody sequences fused to any other sequences, and could have several different meanings, besides the most common usage as set forth above, e.g. chimeric antibody is frequently used interchangeably with humanized antibody.

The claims however are not limited to the common usage meaning of the term. Thus, the specific embodiments intended to be defined by the claims are not known, and one cannot determine the metes and bounds of the claims.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

A. Rejection under 35 USC 112, first paragraph of claims 41-64 pertaining to **lack of enablement for a method for detecting prostate specific reductase, or the protein consisting of amino acids 1-316 of SEQ ID NO:2** remains for reasons already of record in paper of 12/02/04.

Applicant argues that since the expression of the claimed prostatic specific reductase (PSR) protein is limited to the prostate and that detection of PSR protein in cells other than the prostate cells is indicative of metastases of prostate cancer.

Applicant argues that the claimed polypeptide of SEQ ID NO:2 is 98% similar to the prostate short-chain dehydrogenase/reductase(PSDR1) taught by Lin et al, 2001, which is highly expressed in prostate relative to any other tissue, and is detected in all of the normal and neoplastic prostate tissues. Applicant argues that Lin et al also teach that genes and their cognate proteins whose expression is specific for the prostate have greatly added to diagnosis and treatment of prostate carcinoma.

Applicant's arguments set forth in paper of 03/02/05 have been considered but are not deemed to be persuasive for the following reasons:

Although the claimed polypeptide of SEQ ID NO:2 is expressed in a prostate-specific manner, it is unpredictable that one could use the claimed polypeptide for detecting metastasized prostate cells, because it is unpredictable that metastasized prostate cells still express the claimed sequence, because expression of a sequence could be lost during the progression toward metastasis, as taught by Kibel et al, Zhau et al, Cheung et al, Ren et al, and Gingrich et al (all of record, see discussion of these references below, on pages 11-13, in response to Applicant's arguments).

Further, although Lin et al teach that several genes and their cognate proteins whose expression is specific for the prostate have greatly added to diagnosis and treatment of prostate carcinoma, these genes and proteins are different from SEQ ID NO:2, and one cannot predict that SEQ ID NO:2 would have the same properties or

expression, for example during metastasis, because properties and expression of different genes are independent of each other.

In addition, it is noted that the PSDR1 taught by Lin et al **has not** been shown to be overexpressed in prostate cancer tissues as compared to normal prostate tissues, and thus the issue of whether SEQ ID NO:2 is related the PSDR1 taught by Lin et al and has similar expression as the PSDR1, based on 98% sequence similarity is not germane here.

Moreover, one cannot predict the use of the claimed method as a method for detecting a reductase, as implied in Applicant's response that SEQ ID NO:2 is a reductase, because it has 98% similarity in sequence to the reductase PSDR1 taught by Lin et al, because, based on sequence similarity to the reductase PSDR1, one cannot predict that SEQ ID NO:2 is a reductase. It is recognized in the art that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. In particular, Skolnick, et al (Trends in Biotechnology 18: 34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, Sequence-based approaches to function prediction). Skolnick et al state that "Knowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (see Box 2, page 36). In agreement, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting

protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Such concerns are also echoed by Doerks et al.

(1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, similarity in function cannot be reliably inferred based only on sequence identity/similarity between the claimed invention of SEQ ID NO:2 and the reductase PSDR1 taught by Lin et al.

Further, as set forth in the previous Office action, the identification of the polynucleotide encoding the polypeptide of SEQ ID NO:2 in prostate cancer but not normal librairies in the selected, incomplete pool of sequenced clones appears to be a serendipitous event. The fact that the claimed polynucleotide is not expressed in one pool of sequenced clones or is expressed in another appears to be an artifact of the analytical system and cannot be extrapolated to a prediction of whether that molecule is

expressed in the tissue "represented" by the library. It is not possible to determine from the information in the specification whether SEQ ID NO:2 could be useful in prostate cancer detection.

Therefore, since it is not possible to determine from the information in the specification whether SEQ ID NO:2 is overexpressed in prostate cancer tissues, or in metastatic prostate cancer, as compared to normal prostate tissues, one would not know how the use the claimed method.

B. If Applicant could overcome the above 112, first paragraph, Rejection under 35 USC 112, first paragraph of claims 41-64 pertaining to **lack of enablement for a method for detecting prostate specific reductase "variants" of SEQ ID NO:2** still remains for reasons already of record in paper of 12/02/04.

Applicant argues that antibodies that "specifically bind" a particular protein might also capable of binding that protein in a variety of forms, such as orthologues, splice variants, and allelic variants, via a common specific antigenic epitope to which the antibody binds. Applicant argues that the ability of an antibody to bind a protein or its variants would depend on the presence of the specific antigenic epitope to which the antibody binds.

Applicant's arguments set forth in paper of 03/02/05 have been considered but are not deemed to be persuasive for the following reasons:

Although the antibody that binds specifically to a protein consisting of amino acid residues 1-316 of SEQ ID NO:2, could also binds to its variants via a common specific epitope, one cannot predict that the variants of SEQ ID NO:2 would have the same

expression pattern as that of SEQ ID NO:2. It is well known in the art that the variants do not necessarily express in the same pattern as the wild type parent sequence. For example, Schmid S et al, 2001, J comparative Neurology, 430(2): 160-71, teach that the variants flip/flop of the gene GluR are expressed at higher levels in neurons in the auditory braistem, as compared to the wild type GluR-A and GluR-B, and that neurons in the central nucleus of the inferior collicullus express high levels of GluR-B flip but only low levels of the other receptor subunits. Conner et al, 1996, Mol Brain Res, 42: 1-17, teach that full length trkB is found the hippocampus in patients with Alzheimer's disease, but not in hippocampi of either normal age-matched individual or patients with Huntington's disease, and that truncated trkB is found in senile plaques in hippocampus and temporal lobe in both patients with Alzheimer's disease and Huntington's disease, but not in normal brains of aged-matched individuals (page 8, item 3.1.2).

Therefore, even if SEQ ID NO:2 is overexpressed in prostate cancer tissues or metastatic prostate cancer as compared to normal prostate tissue, one cannot predict that variants of SEQ ID NO:2 is overexpressed in prostate cancer tissues or metastatic prostate cancer as compared to normal prostate tissue, and because of this, one would not know how to use the claimed method.

Applicant recites case law, and argues that although the predictability of that art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of whether SEQ ID NO:2 or its variants is overexpressed in prostate cancer tissues, or in metastatic cells as compared to normal prostate tissue, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

C. If Applicant could overcome the above 112, first paragraph, Rejection under 35 USC 112, first paragraph of claims 41-48, 51 still remains, for lack of enablement for a method for detecting prostate specific reductase in any biological sample, any tissue or any cells or saliva remains for reasons already of record in paper of 12/02/04.

Applicant argues that the cited references do not support the proposition that undue experimentation would be required to practice the claimed methods because it is unpredictable that metastatic prostate cells still express the claimed sequence.

(I) Applicant argues that Kibel et al teach that gene inactivation in the 12p12-13 region is a primary feature of both prostate tumors and metastatic foci. Applicant argues that the specification discloses that PSR is expressed in stage C human prostate cancer, the stage at which the cancer has extended beyond the capsule that surrounds the prostate gland. Applicant further argues that Lin et al teach that PSR gene maps to chrosome 14q23-24.3, not to chromosome 12.

Applicant's arguments set forth in paper of 03/02/05 have been considered but are not deemed to be persuasive for the following reasons:

Contrary to Applicant arguments, the cited references support the unpredictability that whether metastatic prostate cells overexpress or still express SEQ ID NO:2.

Kibel, AS et al, 2000, J urol, 164(1): 192-6 teach that gene expression in the chromosomal region 12p12-13 is different in primary and metastatic prostate cancer cells, and that inactivation in the chromosome region 12p12-13 occurs prior to metastasis.

Further, although SEQ ID NO:2 is expressed in seven clones of a prostatic cDNA library of Stage C prostate cancer, one cannot predict that said clones are from metatastic prostate cancer cells.

The specification discloses that SEQ ID NO:2 is found in seven clones of a total of 3397 sequenced clones from a prostatic cDNA library of Stage C prostate cancer (p.11 and Table 1 from page 11).

It is noted that although stage C prostate cancer has some immediate extraprostatic extension, such as the presence of metastatic prostate cancer cells in prostatic capsule, fibromuscular stroma, seminal vesicle, the base of the gland at the neurovascular bundle, and the apex (Lee F et al, 1991, Cancer, 67 (4 supp): 1132-42, abstract), the specification does not disclose where the tissue used for constructing the library is from, i.e. it is not clear whether the tissue used for constructing the library is from the prostate tissue per se, or from prostatic capsule, fibromuscular stroma, seminal vesicle, the base of the gland at the neurovascular bundle, and the apex. Thus, it is not clear whether the library contains any of the cells from the extraprostatic extension, and whether the library contains mainly prostate tissue per se. One cannot predict whether the prostate tissue per se contains a high percentage of metastatic prostate cancer cells such that the metastatic prostate cancer cells are representive of the cDNA library. Thus one cannot predict whether the seven clones from 3397 sequenced clones are from primary prostate cancer cells or metastatic prostate cancer cells. Because of this, one cannot predict whether metastatic prostate cancer cells such as those from extraprostatic extension still express SEQ ID NO:2.

This unpredictability would thus apply as well to metastatic cells that are in the blood or in any tissue other than prostate tissue, especially further changes in gene

expression could occur as prostate cancer progresses into later stages beyond the immediate extraprostatic extension.

Further, although the reductase PSDR1 taught by Lin et al is not on chromosome 12, where the inactivation of genes occurs during the progression of primary prostate cancer cells to metastatic prostate cancer cells, one cannot predict that the claimed SEQ ID NO:2 is not mapped on chromosome 12, because one cannot predict that SEQ ID NO:2 has the same properties and function as the reductase PSDR1 taught by Lin et al, based on 98% sequence similarity, supra.

(II) Applicant argues that concerning the teaching of Zhau et al, even if the PSR expression were downregulated during transition from metastasis, this would not preclude the use of the claimed method in diagnosis of prostate cancer, since PSR is predominantly expressed in prostate and prostate derived tissue over other tissue.

This is not found to be persuasive. Zhau et al teach that there is chromosomal translocation in metastatic prostate cells. One cannot thus predict whether such chromosomal translocation would eliminate the expression of SEQ ID NO:2 in metastatic prostate cells.

(III) Applicant argues that concerning the teaching of Cheung et al, Ren et al, and Ginrich et al, none of down-regulated genes appear to correspond to the PSR of the claimed invention, and that even if the PSR expression were down-regulated during transition from metastasis, this would not preclude the use of the claimed method in diagnosis of prostate cancer, since PSR is predominantly expressed in prostate and prostate derived tissue over other tissue.

This is found not to be persuasive. The references by Cheung et al, Ren et al, and Ginrich et al are recited to show that the level of gene expression is unpredictable during progression to metastasis, and thus one cannot predict whether SEQ ID NO:2 is expressed in metastatic prostate cells.

Because of this one cannot predict that the claimed method could be used with any biological sample, any tissue, any cells or saliva.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS
May 12, 2005

SUSAN UNGAR, PH.D
PRIMARY EXAMINER